VACCINOLOGY – A PUBLIC HEALTH REVOLUTION

M.D. THESIS

"If you asked a public health professional to draw up a top-ten list of the achievements of the past century, he or she would be hard pressed not to rank immunisation first. In short, the vaccine represents the single greatest promise of biomedicine: disease prevention."

A Stern

Dr Helen Marshall

MBBS (University of Adelaide)

DCH (Department of Paediatrics, University of Adelaide)

MPH (University of Adelaide)

Director,

Vaccinology and Immunology Research Trials Unit (VIRTU)

Discipline of Paediatrics

School of Paediatrics and Reproductive Health

Women's and Children's Hospital

South Australia

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Table of Contents

Abstract

This thesis comprises a collection of publications on new vaccines, vaccine safety and research in implementation of new vaccines into the community to inform public health policy globally. The papers presented outline my research experience in vaccinology which has been conducted in collaboration with a number of national and international colleagues, who are included as coauthors. I have been involved in all aspects of the research including study concepts, conduct, analysis and interpretation of the results and manuscript preparation and publication.

Studies in investigational vaccines outlined in Chapters 1, 2 and 4 were conducted as multicentre studies on the immunogenicity and safety of new vaccines including DTPa-HBV-Hib (diphtheria, tetanus, acellular pertussis, hepatitis B and *Haemophilus influenzae* type b) vaccine, DTPa-HBV-IPV (diphtheria, tetanus, acellular pertussis, hepatitis B and inactivated polio) vaccine, live intranasal attenuated influenza vaccine, Hib-MenCY (*Haemophilus influenzae* type b, *Neisseria meningitidis* serogroups C and Y) vaccine, DTPa-IPV (diphtheria, tetanus, acellular pertussis and inactivated polio) vaccine, PIV3 (parainfluenza virus type 3) vaccine and RSV-PIV3 (respiratory syncytial virus and parainfluenza type 3 virus) vaccine. Many of these vaccines are now licensed in Australia (DTPa-HBV-IPV; "Infanrix-Penta", DTPa-IPV; "InfanrixIPV", HepAB; "Twinrix") with some licensed in other countries (live attenuated influenza vaccine; "FluMist") and others soon to be licensed (Hib-MenCY) or still in clinical development (PIV3, RSV-PIV3).

Licensing of vaccines has been dependent on provision of clinical data of an excellent standard, resulting from clinical studies conducted according to ICH-GCP (International Conference on Harmonisation – Good Clinical Practice) as included in this thesis. Currently, the cost of bringing a vaccine from the laboratory bench to the market is around $1 billion, with much of this cost derived from extensive clinical trial testing undertaken, often directed or influenced by regulatory authorities.

Studies for neonates, young children and adolescents require specific approaches relevant to their needs. Important areas such as recruitment to studies, levels of understanding, needs of families and caregivers, and appropriate care of potentially fearful and tearful participants all need to be addressed carefully and with great skill and support. Issues of assessment of symptoms and potential adverse effects need to be approached differently to those in older independent study participants. Paediatric vaccine clinical trials

can only be successfully conducted with a specialized, experienced and dedicated team of investigators with a wide range of individual skills. Each investigational participant age group requires a specific type of specialist expertise, including skills which may range from venesection of a 2 month old infant (preferably on the first attempt), to blowing bubbles to distract an anxious 4 year old being vaccinated to discussing the study requirement for urine pregnancy testing (as part of study exclusion criteria) to a 12 year old girl. The successful completion of a paediatric vaccine study is dependent on staff that can provide ethical judgement and the required support and consideration for families that are willing to be involved in vaccinology research for the public good. There are only a select group of paediatric vaccinology centres in Australia of which our unit is included. Conducting investigational vaccine trials in Australia has the advantage of providing immunogenicity and safety data in Australian children to Australian regulatory authorities and immunisation expert groups such as the Australian Technical Advisory Group on Immunisation (ATAGI) to inform the optimal immunisation schedule for the Australian population.

Community engagement in and acceptance of new vaccines introduced into the community underpins the success of immunisation programs. Results of social epidemiological studies conducted to examine the introduction of vaccines including varicella, human papillomavirus, and pandemic influenza vaccines are outlined in Chapter 3. Understanding community awareness of vaccines and concerns about vaccine safety is essential for the planning and development of vaccine delivery programs whether delivered through schools, doctors or local government. Results of these studies showed low knowledge of Human Papillomavirus disease and vaccination in the community but acceptance of this cancer preventing strategy if the vaccine was deemed to be safe. Likewise knowledge of pandemic influenza was poor but acceptance of strategies to prevent transmission of infection was assured. Poor uptake of varicella vaccine following licensing was primarily due to poor knowledge about availability of the vaccine and cost of the vaccine prior to funding. Results of these studies have been used to inform public health policy in relation to vaccine delivery to the community.

Continuous review of the Australian National Immunisation Program is required to ensure optimal uptake, timely delivery and acceptability of vaccines. Studies in Chapter 5 outline new strategies to reduce the number of injections required to complete an immunisation schedule while ensuring optimal protection, to reduce the burden of disease in our community.

The work presented in this thesis has supported the timely introduction of new vaccines with knowledge of the community's concerns and acceptance of these vaccines to direct optimal service delivery to achieve high vaccine uptake and reduction in the burden of disease for current and future generations.